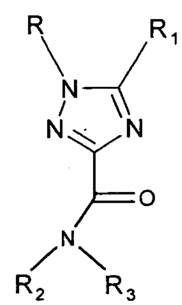
1H-1,2,4-Triazole-3-carboxamide derivatives having cannabinoid-CB_1 receptor agonistic, partial agonistic, inverse agonistic or antagonistic activity

The present invention relates to a group of 1H-1,2,4-triazole derivatives, to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active ingredient.

These 1H-1,2,4-triazole-carboxamide derivatives are potent cannabinoid-CB_1 receptor agonists, partial agonists, inverse agonists or antagonists, useful for the treatment of psychiatric and neurological disorders, as well as other diseases involving cannabinoid-CB_1 neurotransmission.

1,5-Diaryl-1H-1,2,4-triazole-3-carboxamide derivatives have been described in EP 0346620 and GB 2120665 as herbicides. Recently 1,2,4-triazoles were described as potential agonists and antagonists of cannabinoid-CB_1 and –CB_2 receptors (Jagerovic, N. *et al.*, *Drugs Fut.* **2002**, 27(Suppl. A): XVIIth Int. Symp. on Medicinal Chemistry, P284)

It has now surprisingly been found that known and new 1,5-diaryl-1H-1,2,4-triazole-3-carboxamide derivatives of the formula (I), as well as prodrugs, salts, and stereo-isomers thereof, are potent antagonists, agonists, inverse agonists or partial agonists of the cannabinoid CB_1 receptor:



(I)

wherein

- R and R_1 independently represent a phenyl, naphtyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl or triazinyl group, which groups may be substituted with 1-4 substituents X, which can be the same or different, from the group branched or unbranched (C_{1-3})-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C_{1-2})-amino, mono- or dialkyl (C_{1-2})-amido,

(C_{1-3})-alkoxycarbonyl, trifluoromethylsulfonyl, sulfamoyl, (C_{1-3})-alkylsulfonyl, carboxyl, cyano, carbamoyl, (C_{1-3})-dialkylaminosulfonyl, (C_{1-3})-monoalkylamino-sulfonyl and acetyl,

- R_2 represents a hydrogen atom or a branched or unbranched C_{1-8} alkyl or C_{1-8} cycloalkyl-alkyl group or a phenyl, benzyl or phenethyl group which aromatic rings may be substituted with 1-4 substituents X, wherein X has the meaning as indicated above, or R_2 represents a pyridyl or thienyl group,
- R_3 represents branched or unbranched C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-8} cycloalkyl, C_{5-10} bicycloalkyl, C_{6-10} tricycloalkyl, C_{3-8} alkenyl, C_{5-8} cycloalkenyl, which groups may optionally contain one or more heteroatoms from the group (O, N, S), which groups may be substituted with a hydroxy group, an ethynyl group or 1-3 fluoro atoms, or R_3 represents a phenyl, benzyl or phenethyl group which aromatic rings may be substituted with 1-4 substituents X, wherein X has the meaning as indicated above, or R_3 represents a pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl or thienyl group which heteroaromatic rings may be substituted with 1-2 substituents X, wherein X has the meaning as indicated above, or R_3 represents a group NR_4R_5 wherein R_4 and R_5, together with the nitrogen atom to which they are bonded, form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic moiety having 4 to 10 ring atoms, which heterocyclic group contains one or two heteroatoms from the group N, O or S, which heteroatoms can be the same or different, which heterocyclic moiety may be substituted with a branched or unbranched C_{1-3} alkyl, hydroxy or trifluoromethyl group or a fluoro atom, or

  R_2 and R_3, together with the nitrogen atom to which they are bonded, form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic moiety having 4 to 10 ring atoms, which heterocyclic group contains one or two heteroatoms from the group N, O or S, which heteroatoms can be the same or different, which heterocyclic moiety may be substituted with a branched or unbranched C_{1-3} alkyl, hydroxy, piperidinyl or trifluoromethyl group or a fluoro atom.

A group of four 1,5-diaryl-1H-1,2,4-triazole-3-carboxamide derivatives in which the amide N-atom is part of an unsubstituted piperidinyl or morpholinyl group is described by D. Clerin and J.P. Fleury in *Bull. Soc. Chim. Fr.*, **1974**, 1-2, Pt.2, 211-217.

1-(4-Methylphenyl)-5-phenyl-N-(2-pyridyl)-1H-1,2,4-triazole-3-carboxamide is described by M. H. Elnagdi et al. in *Heteroatom Chem.*, **1995**, *6*, 589-592.

A group of four 1,5-diaryl-N-(2-pyridyl)-1H-1,2,4-triazole-3-carboxamides is described by A. H. Harhash et al. in *Indian J. Chem.*, **1976**, *14B*, 268-272.

Due to the potent cannabinoid-CB_1 receptor agonistic, partial agonistic, inverse agonistic or antagonistic activity the compounds of the invention are suitable for use in the treatment of psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, addiction, appetence, drug dependence, neurodegenerative disorders, dementia, dystonia, muscle spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, neuroinflammatory disorders, plaque sclerosis, viral encephalitis, demyelinisation related disorders, as well as for the treatment of pain disorders, including neuropathic pain disorders, septic shock, glaucoma, diabetes, cancer, emesis, nausea, gastrointestinal disorders, gastric ulcers, diarrhoea and cardiovascular disorders.

The affinity of the compounds of the invention for cannabinoid CB_1 receptors was determined using membrane preparations of Chinese hamster ovary (CHO) cells in which the human cannabinoid CB_1 receptor is stably transfected in conjunction with $[^3H]$CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the $[^3H]$-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting.

The cannabinoid CB_1 receptor antagonistic, agonistic or partial agonistic activity of compounds of the invention was determined by functional studies using the human CB_1 receptor cloned in Chinese hamster ovary (CHO) cells. CHO cells were grown in a DMEM culture medium, supplemented with 10% heat-inactivated fetal calf serum. Medium was aspirated and replaced by DMEM, without fetal calf serum, but containing $[^3H]$-Arachidonic acid and incubated overnight in a cell culture stove (5% CO_2/95% air; 37 °C; water-saturated atmosphere). During this period $[^3H]$-Arachidonic acid was incorporated in membrane phospholipids. On the test day, medium was aspirated and cells were washed three times using 0.5 ml phosphate-buffered saline, containing 0.2% bovine serum albumin. Stimulation of the CB_1 receptor

by WIN 55,212-2 led to activation of PLA_2 followed by release of [^{3}H]-Arachidonic acid into the medium. This WIN 55,212-2-induced release was concentration-dependently antagonized by CB_1 receptor antagonists.

Cannabinoid agonistic or partial agonistic activity of compounds of the invention can be determined according to published methods, such as assessment of *in vivo* cannabimimetic effects (Wiley, J. L.; Jefferson, R. G; Grier, M. C.; Mahadevan, A.; Razdan, R. K.; Martin, B. R. *J. Pharmacol. Exp. Ther.* **2001**, *296*, 1013).

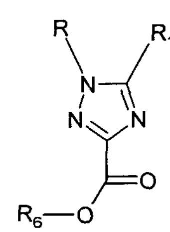
The invention relates both to racemates, mixtures of diastereomers and the individual stereoisomers of the compounds having formula (I). Also prodrugs, i.e. compounds which when administered to humans by any known route, are metabolised to compounds having formula (I), belong to the invention. In particular this relates to compounds with primary or secondary amino or hydroxy groups. Such compounds can be reacted with organic acids to yield compounds having formula (I) wherein an additional group is present which is easily removed after administration, for instance, but not limited to amidine, enamine, a Mannich base, a hydroxyl-methylene derivative, an O-(acyloxymethylene carbamate) derivative, carbamate, ester, amide or enaminone.A pro-drug is an inactive compound, which when absorbed is converted into an active form (Medicinal Chemistry: Principles and Practice, 1994, ISBN 0-85186-494-5, Ed.: F. D. King, p. 216).

The compounds of the invention can be brought into forms suitable for administration by means of usual processes using auxiliary substances and/or liquid or solid carrier materials.

Suitable synthetic routes for the compounds of the invention are the following:

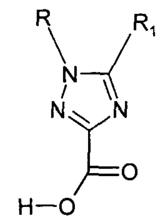
Synthetic route A

Step 1: Ester hydrolysis of a compound having formula (II) wherein R_6 represents a branched or unbranched (C_{1-4})-alkyl group or a benzyl group,



(II)

yields a compound having formula (III)



(III)

wherein R and R_1 have the meanings as described above.

The compounds of the invention having formula (II), wherein R_6 represents a branched or unbranched alkyl group (C_{1-4}) or benzyl group can be obtained according to methods known, for example:

a) Sawdey, G.W. *J. Am. Chem. Soc.* **1957**, *79*, 1955
b) Czollner, L. *et al.*, *Arch. Pharm. (Weinheim)* **1990**, *323*, 225
c) Eicher, T. and Hauptmann, S. *The Chemistry of Heterocycles*, Thieme Verlag, Stuttgart, **1995** (ISBN 313 100511 4), p. 208-212.

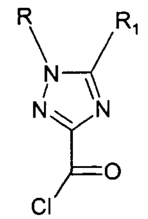
Step 2: Reaction of a compound having formula (III) with a compound having formula R_2R_3NH wherein R_2 and R_3 have the meanings as described above *via* activating and coupling methods such as formation of an active ester, or in the presence of a coupling reagent such as DCC, HBTU, BOP, CIP (2-chloro-1,3-dimethylimidazolinium hexafluorophosphate) or PyAOP (7-azabenzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate). Activating and coupling methods of this type are described in

a) M. Bodanszky and A. Bodanszky: *The Practice of Peptide Synthesis*, Springer-Verlag, New York, **1994**; ISBN: 0-387-57505-7;
b) K. Akaji *et al.*, *Tetrahedron Lett.* (**1994**), 35, 3315-3318);
c) F. Albericio *et al.*, *Tetrahedron Lett.* (**1997**), 38, 4853-4856).

This reaction gives a 1H-1,2,4-triazole derivative having formula (I).

Synthetic route B

A compound having formula (III) is reacted with a halogenating agent such as thionyl chloride ($SOCl_2$) or oxalyl chloride. This reaction yields the corresponding carbonyl chloride (acid chloride) (IV).



(IV)

Reaction of a compound having formula (IV) with a compound having formula R_2R_3NH wherein wherein R_2 and R_3 have the meanings as described above gives a 1H-1,2,4-triazole derivative having formula (I).

Synthetic route C

A compound having formula (II) is reacted in an amidation reaction with a compound having formula R_2R_3NH wherein R_2 and R_3 have the meanings as described hereinabove to give a 1H-1,2,4-triazole derivative having formula (I). Such amidation reactions can be promoted by the use of trimethylaluminum $Al(CH_3)_3$ (For more information on aluminum-mediated conversion of esters to amides, see: J. I. Levin, E. Turos, S. M. Weinreb, *Synth Commun.* (1982), *12*, 989-993.)

<u>Example I</u>

Part A: To a stirred solution of dimethyl aminomalonate hydrochloride (25 gram, 0.136 mol) in dichloromethane (200 mL) triethylamine (41.4 mL, 2.2 molar equivalent) is added at 0 °C. 4-Chlorobenzoyl chloride (23.8 gram, 0.136 mol) is slowly added and the resulting solution is allowed to stand at room temperature overnight. Water is added and the organic layer is separated. The water layer is extracted twice with dichloromethane. The collected organic layers are washed with water, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is recrystallised from methanol (400 mL) to give dimethyl 2-(4-chlorobenzoylamino)malonate (30.5 gram, 79 % yield). Melting point: 146-148 °C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.86 (s, 6H), 5.38 (d, J = 6 Hz, 1H), 7.15 (br d, J ~ 6 Hz, 1H), 7.43 (d, J = 8 Hz, 2H), 7.79 (d, J = 8 Hz, 2H).

Part B: To a stirred suspension of 2,4-dichloroaniline (19.44 gram, 0.12 mol) in concentrated HCl (25 mL) and acetic acid (75 mL) at 0 °C is added a solution of $NaNO_2$ (9.0 gram, 0.13 mol) in water (50 mL) and the resulting solution is stirred for 15 minutes. A solution of dimethyl 2-(4-chlorobenzoylamino)-malonate (28.55 gram, 0.10 mol) in acetone (200 mL) is slowly added while keeping the temperature below 0 °C. A solution of K_2CO_3 (120 gram) in water (200 mL) is slowly added and the resulting black mixture is stirred for 30

minutes at 0 °C. The mixture is extracted three times with EtOAc. The collected organics are washed with water, aqueous $NaHCO_3$ and water, respectively, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is dissolved in methanol (500 mL) and a solution of sodium (1 gram) in methanol (75 mL) is added. The resulting stirred mixture is allowed to stand overnight at room temperature and cooled in a refrigerator. The formed precipitate is collected by filtration and washed with methanol to give methyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,4-triazole-3-carboxylate (11.4 gram, 30 % yield). Melting point: 153-154 °C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.07 (s, 3H), 7.28-7.60 (m, 7H).

Part C: To a stirred suspension of methyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,4-triazole-3-carboxylate (11.3 gram, 0.0295 mol) in methanol (100 mL) is added KOH (45 % aqueous solution, 7.5 mL) and the resulting mixture is heated at reflux temperature for 4 hours. The mixture is concentrated in vacuo and water (150 mL) and concentrated HCl are added. The yellow precipitate is collected by filtration, washed with water and dried in vacuo to give 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,4-triazole-3-carboxylic acid (10.0 gram, 92 % yield). Melting point: 141-144 °C (decomposition).

Part D: To a stirred solution of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,4-triazole-3-carboxylic acid (1.48 gram, 4.0 mmol) in acetonitrile (20 mL) is successively added diisopropylethylamine (DIPEA) (1.5 mL, 2.1 molar equivalent), O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) (1.66 gram, 1.1 molar equivalent) and 1-aminopiperidine (0.44 gram, 1.1 molar equivalent). After stirring overnight an aqueous $NaHCO_3$ solution is added. The resulting mixture is three times extracted with dichloromethane. The combined organic layers are washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a crude oil (3.6 gram). This oil is further purified by flash chromatography (silica gel; EtOAc / petroleum ether (40-60 °C) = 7/3 (v/v)). The purified material is treated with ethanolic HCl (1M solution) to give 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(piperidin-1-yl)-1H-1,2,4-triazole-3-carboxamide hydrochloride (1.50 gram, 77 % yield). Melting point: 238-240 °C (decomposition). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.46-1.54 (m, 2H), 1.78-1.85 (m, 4H), 3.22-3.28 (m, 4H), 7.50 (s, 4H), 7.70 (dd, J = 8 and 2 Hz, 1H), 7.85-7.87 (m, 1H), 7.91 (d, J = 8 Hz, 1H), (NH not visible).

Analogously were prepared the examples 2-18:

2. 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-N-(pyrrolidin-1-yl)-1H-1,2,4-triazole-3-carboxamide hydrochloride. Melting point: 248-255 °C (decomposition).
3. 5-(4-Chlorophenyl)-N-cyclohexyl-1-(2,4-dichlorophenyl)-1H-1,2,4-triazole-3-carboxamide. Melting point: 186-188 °C.
4. N-t-Butoxy-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,4-triazole-3-carboxamide. Melting point: 150-152 °C.
5. 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-N-(n-pentyl)-1H-1,2,4-triazole-3-carboxamide. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.92 (t, J = 7 Hz, 3H), 1.35-1.44 (m, 4H), 1.62-1.70 (m, 2H), 3.48-3.56 (m, 2H), 7.20-7.25 (m, 1H), 7.34 (dt, J = 8 and 2 Hz, 2H), 7.42-7.50 (m, 4H), 7.54 (d, J = 2 Hz, 1H).
6. 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-N-(morpholin-4-yl)-1H-1,2,4-triazole-3-carboxamide. Melting point: 184-186 °C.
7. 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-N-(piperidin-1-yl)-1H-1,2,4-triazole-3-carboxamide hydrochloride. Melting point: 234-237 °C (decomposition).
8. 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-N-(pyrrolidin-1-yl)-1H-1,2,4-triazole-3-carboxamide hydrochloride. Melting point: 234-236 °C (decomposition).
9. 1-(4-Chlorophenyl)-N-cyclohexyl-5-(2,4-dichlorophenyl)-1H-1,2,4-triazole-3-carboxamide. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.14-1.81 (m, 8H), 2.02-2.10 (m, 2H), 4.00-4.11 (m, 1H), 7.08 (br d, J ~ 7 Hz, 1H), 7.26 (br d, J ~ 8 Hz, 2H), 7.34 (br d, J ~ 8 Hz, 2H), 7.40 (dd, J = 8 and 2 Hz, 1H), 7.44-7.48 (m, 2H).
10. N-t-Butoxy-1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-1H-1,2,4-triazole-3-carboxamide. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 9H), 7.25 (br d, J ~ 8 Hz, 2H), 7.35 (br d, J ~ 8 Hz, 2H), 7.41 (dd, J = 8 and 2 Hz, 1H), 7.44-7.48 (m, 2H), 9.18, br s, 1H).
11. 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-N-(n-pentyl)-1H-1,2,4-triazole-3-carboxamide. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.91 (t, J = 7 Hz, 3H), 1.35-1.41 (m, 4H), 1.60-1.70 (m, 2H), 3.48-3.56 (m, 2H), 7.21 (br t, J ~ 7 Hz, 1H), 7.26 (br d, J ~ 8 Hz, 2H), 7.34 (br d, J ~ 8 Hz, 2H), 7.40 (dd, J = 8 and 2 Hz, 1H), 7.44-7.48 (m, 2H).
12. 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-N-(morpholin-4-yl)-1H-1,2,4-triazole-3-carboxamide hydrochloride. Melting point: 224-226 °C.
13. 1-(2,4-Dichlorophenyl)-5-(pyridin-2-yl)-N-(piperidin-1-yl)-1H-1,2,4-triazole-3-carboxamide. Melting point: 191-193 °C.
14. 5-(2,4-Dichlorophenyl)-N-(piperidin-1-yl)-1-(4-(trifluoromethyl)phenyl)-1H-1,2,4-triazole-3-carboxamide. Melting point: 159-161 °C.

15. 1'-[5-(2,4-dichlorophenyl)-1-(4-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-3-yl)carbonyl]piperidine. Melting point: 155-156 °C.

16. 1-(2,4-Dichlorophenyl)-N-(piperidin-1-yl)-5-(pyridin-3-yl)-1H-1,2,4-triazole-3-carboxamide. Melting point: 219 °C.

17. 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-N-(5,5,5-trifluoropentyl)-1H-1,2,4-triazole-3-carboxamide. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.63-1.80 (m, 4H), 2.06-2.22 (m, 2H), 3.54 (q, J ~ 7 Hz, 2H), 7.26 (m, 3H), 7.34 (br d, J ~ 8 Hz, 2H), 7.40 (dd, J = 8 and 2 Hz, 1H), 7.44-7.48 (m, 2H).

18. 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-N-(5-fluoropentyl)-1H-1,2,4-triazole-3-carboxamide. ^{1} H-NMR (400 MHz, $CDCl_3$): δ 1.63-1.80 (m, 4H), 2.06-2.22 (m, 2H), 3.54 (q, J ~ 7 Hz, 2H), 7.22-7.28 (m, 3H), 7.34 (br d, J ~ 8 Hz, 2H), 7.40 (dd, J = 8 and 2 Hz, 1H), 7.44-7.48 (m, 2H).

Example 19

Part A: 1-(Chlorophenyl)-5-(2,4-dichlorophenyl)-1H-1,2,4-triazole-3-carboxylic acid was prepared analogously to the procedure as described in Example 1, Part A-C by using dimethyl aminomalonate hydrochloride, 2,4-dichlorobenzoyl chloride and 4-chloroaniline as starting materials, respectively. Melting point: 102-104 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.36 (br d, J ~ 8 Hz, 2H), 7.50 (br d, J ~ 8 Hz, 2H), 7.59 (dd, J = 8 and 2 Hz, 1H), 7.70 (d, J = 2 Hz, 1H), 7.75 (d, J = 8 Hz, 1H), OH proton is part of water peak at δ 3.4.

Analogously was 1-(chlorophenyl)-5-(2,5-dichlorophenyl)-1H-1,2,4-triazole-3-carboxylic acid prepared by using dimethyl aminomalonate hydrochloride, 2,5-dichlorobenzoyl chloride and 4-chloroaniline as starting materials, respectively. Melting point: 183-188 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.41 (br d, J ~ 8 Hz, 2H), 7.52 (br d, J ~ 8 Hz, 2H), 7.56 (d, J = 8 Hz, 1H), 7.65 (dd, J = 8 and 2 Hz, 1H), 7.88 (d, J = 2 Hz, 1H), OH proton is part of water peak at δ 3.5.

Part B: To a stirred solution of 1-(chlorophenyl)-5-(2,4-dichlorophenyl)-1H-1,2,4-triazole-3-carboxylic acid (0.37 g, 1.00 mmol) in dichloromethane (10 mL) is added oxalyl chloride (0.254 g, 2.00 mmol). The resulting mixture is concentrated in vacuo to give crude 1-(chlorophenyl)-5-(2,4-dichlorophenyl)-1H-1,2,4-triazole-3-carbonyl chloride.

Part C: The crude 1-(chlorophenyl)-5-(2,4-dichlorophenyl)-1H-1,2,4-triazole-3-carbonyl chloride is dissolved in tetrahydrofuran (THF) (10 mL). 2,3-Dihydro-1H-inden-2-ylamine (0.40 g, 3.00 mmol) is added and the resulting solution is stirred for 42 hours at 25 °C. The mixture is concentrated in vacuo and the residue is purified by preparative liquid chromatography to give pure 1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-N-(2,3-dihydro-1H-inden-2-yl)-1H-1,2,4-triazole-3-carboxamide (393 mg, 81 % yield). MS (ESI$^+$) 485.6. ^{1}H-NMR (400 MHz, DMSO-d_6): 3.06 (dd, J = 16 and 8 Hz, 2H), 3.21 (dd, J = 16 and 8 Hz,

2H), 4.71-4.82 (m, 1H), 7.12-7.16 (m, 2H), 7.19-7.24 (m. 2H), 7.39 (br d, J ~ 8 Hz, 2H), 7.52 (br d, J ~ 8 Hz, 2H), 7.60 (dd, J = 8 and 2 Hz, 1H), 7.71 (d, J = 2 Hz, 1H), 7.79 (d, J = 8 Hz, 1H), 8.93-8.97 (m, 1H, NH).

Analogously were prepared the examples 20-43:

20. 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-N-(1-ethynylcyclohexyl)-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 473.3.
21. 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-N-(2-methylcyclohexyl)-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 465.5.
22. 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-N-(4-methylcyclohexyl)-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 465.5.
23. 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-N-cyclooctyl-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 477.3.
24. 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-N-(azepan-1-yl)-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 466.4.
25. 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-N-cycloheptyl-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 465.5.
26. N-t-Butyl-1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 425.4.
27. 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-N-(1,1-diethylprop-2-yn-1-yl)-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 461.5.
28. 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-N-(2,2,2-trifluoroethyl)-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 451.3.
29. 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-N-(exo-bicyclo[2.2.1]hept-2-yl)-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 461.5.
30. 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-N-(4-(2-propyl)piperazin-1-yl)-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 480.3. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.00 (d, J = 7 Hz, 6H), 2.46-2.56 (m, 4H), 2.72 (septet, J = 7 Hz, 1H), 3.66-3.74 (m, 4H), 7.36 (br d, J = 8 Hz, 2H), 7.51 (br d, J = 8 Hz, 2H), 7.59 (dd, J = 8 and 2 Hz, 1H), 7.72 (d, J = 2 Hz, 1H), 7.75 (d, J = 8 Hz, 1H).
31. 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-N-(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 476.4.
32. 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-N-pentyl-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 435.5.
33. 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-N-(2,2-dimethylpropyl)-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 439.6.
34. 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-N-(3-(trifluoromethyl)phenyl)-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 511.7.

35. 1'-[1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-1H-1,2,4-triazol-3-yl)carbonyl]-1,4'-bipiperidine. MS (ESI^+) 520.5.
36. 1-(4-Chlorophenyl)-N-(4-chlorophenyl)-5-(2,5-dichlorophenyl)-N-methyl-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 491.4.
37. 1-(4-Chlorophenyl)-5-(2,5-dichlorophenyl)-N-(1-ethynylcyclohexyl)-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 473.4.
38. 1-(4-Chlorophenyl)-5-(2,5-dichlorophenyl)-N-(2-methylcyclohexyl)-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 465.5.
39. 1-(4-Chlorophenyl)-5-(2,5-dichlorophenyl)-N-(4-methylcyclohexyl)-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 465.6.
40. 1-(4-Chlorophenyl)-5-(2,5-dichlorophenyl)-N-cyclooctyl-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 477.3.
41. 1-(4-Chlorophenyl)-5-(2,5-dichlorophenyl)-N-cycloheptyl-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 465.6.
42. 1-(4-Chlorophenyl)-5-(2,5-dichlorophenyl)-N-cyclopentyl-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 435.5.
43. 1-(4-Chlorophenyl)-5-(2,5-dichlorophenyl)-N-(2,2-dimethylpropyl)-1H-1,2,4-triazole-3-carboxamide. MS (ESI^+) 439.6.

Pharmacological test results of a subset of the compounds of the invention, obtained with the assays described above, are given in the table below:

	Human cannabinoid-CB_1 receptors	
	In vitro affinity	*In vitro* antagonism
Example	**pK_i value**	**pA_2 value**
Example 2	**6.6**	**7.2**
Example 3	**6.9**	**8.7**
Example 5	**6.9**	
Example 9	**7.4**	**8.2**
Example 11	**6.3**	